EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids) , 2015. Scientific Opinion on Flavouring Group Evaluation 65, Revisio n 1 (FGE.65Rev1) : Consideration of sulfur - substituted furan derivatives used as flavouring agents evaluated by JECFA (59th meeting) structurally related to a subgroup of substances within the group of ' Furfuryl and furan derivatives with and without additional side - chain substituents and heteroatoms from chemical group 14' evaluated by JECFA in FGE.13Rev2 (2011)

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SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 65, Revision 1 (FGE.65Rev1): Consideration of sulfur-substituted furan derivatives used as flavouring agents evaluated by JECFA (59th meeting) structurally related to a subgroup of substances within the group of 'Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14' evaluated by EFSA in FGE.13Rev2 (2011)[1]

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids of the European Food Safety Authority was requested to consider evaluations of flavouring substances assessed since 2000 by the Joint FAO/WHO Expert Committee on Food Additives (the JECFA), and to decide whether further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. The substances are evaluated through a stepwise approach that integrates information on structure-activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity. FGE.65 concerns a group of 33 sulfur-substituted furan derivatives evaluated by the JECFA at their 59th meeting. The Panel concluded in FGE.65 that the evaluation could not be finalised for four of the 33 substances [FL-no: 13.056, 13.160, 13.193 and 13.194] due to lack of toxicity data. In the present revision of FGE.65, the toxicity data requested in FGE.65 for [FL-no: 13.160] have now become available. These toxicity data are also considered to cover the evaluation of [FL-no: 13.193 and 13.194], but not [FL-no: 13.056]. Based on the new data the Panel agrees with the JECFA conclusion, 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach for 32 of the furan derivatives. For one substance [FL-no: 13.056] a request for additional toxicity data still remains. Besides the safety assessment of these flavouring substances, the specifications for the materials of commerce have also been considered and for all 33 substances, the information is adequate.

[1] On request from the European Commission, Question No EFSA-Q-2014-00477 to -00479, adopted on 29 January 2015.

[2] Panel members: Claudia Bolognesi, Laurence Castle, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Wim Mennes, Maria Rosaria Milana, André Penninks, Maria de Fatima Tavares Poças, Vittorio Silano, Andrew Smith, Christina Tlustos, Fidel Toldra, Detlef Wölfle and Holger Zorn. Correspondence: fip@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Groups on Flavourings: Ulla Beckman Sundh, Leon Brimer, Karl-Heinz Engel, Rainer Gürtler, Trine Husøy, Wim Mennes, Gerard Mulder and Harriet Wallin for the preparatory work on this scientific opinion and the hearing experts: Vibe Beltoft and Karin Nørby and EFSA staff, Annamaria Rossi, Maria Carfi, Kim Rygaard Nielsen and Maria Anastassiadou for the support provided to this scientific opinion.

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KEY WORDS

sulfur-substituted furan derivatives, JECFA 59th meeting, FGE.65Rev1, FGE.13Rev2

SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) was asked to deliver scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the CEF Panel was requested to consider the Joint FAO/WHO Expert Committee on Food Additives (the JECFA) evaluations of flavouring substances assessed since 2000, and to decide whether no further evaluation is necessary, as laid down in Commission Regulation (EC) No 1565/2000. These flavouring substances are listed in the Register, which was adopted by Commission Decision 1999/217/EC and its consecutive amendments.

The present evaluation deals with 33 substances in the JECFA flavouring group of sulfur-substituted furan derivatives. These substances are structurally related to the group of sulfur-substituted furans evaluated within the group of 'Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14' evaluated by EFSA in Flavouring Group Evaluation 13, Revision 2 (FGE.13Rev2).

The present revision of FGE.65, FGE.65Rev1 is due to the availability of new toxicity data on 2-methyltetrahydrofuran-3-thiol [FL-no: 13.160], requested by the Panel in FGE.65.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for 32 candidate substances included in this FGE. For 23 substances the Panel also agreed with JECFA with respect to the choice of the NOAEL to finalise the evaluation. For nine substances the NOAEL used by JECFA was considered invalid, but the Panel could finalise the evaluations of these substances using NOAELs derived from new or existing data from the candidate substances or for supporting substances. Thus, for 32 substances the Panel reached the same conclusion as JECFA with respect to their use as chemically defined flavouring substances in food. For one substance [FL-no: 13.056] no adequate NOAEL could be identified by the Panel and subsequently, no conclusion as to the safety when used at levels of intake estimated using the MSDI approach could be reached.

For all 33 substances evaluated through the Procedure by the JECFA use levels are needed to calculate the Modified Theoretical Added Maximum Daily Intake (mTAMDI) in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 33 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications: Adequate specifications including complete purity criteria and identity are available for all of the JECFA-evaluated substances.

Thus, the Panel has reservations for one substance [FL-no: 13.056] for which additional toxicity data are needed. For the remaining 32 JECFA-evaluated sulfur-substituted furan derivatives [Fl-nos: 13.015, 13.016, 13.017, 13.026, 13.032, 13.033, 13.040, 13.041, 13.050, 13.051, 13.053, 13.055, 13.056, 13.063, 13.064, 13.071, 13.075, 13.077, 13.078, 13.079, 13.082, 13.086, 13.093, 13.142, 13.151, 13.152, 13.153, 13.160, 13.193, 13.194, 13.196 and 13.197], the Panel agrees with JECFA conclusion 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of flavourings is regulated under Regulation (EC) No 1334/2008 of the European Parliament and Council of 16 December 2008[4] on flavourings and certain food ingredients with flavouring properties for use in and on foods. On the basis of Article 9(a) of this Regulation, an evaluation and approval are required for flavouring substances.

The Union list of flavourings and source materials was established by Commission Implementing Regulation (EC) No 872/2012[5]. The list contains flavouring substances for which the scientific evaluation should be completed in accordance with Commission Regulation (EC) No 1565/2000[6].

On 25 November 2009, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) adopted an opinion on Flavouring Group Evaluation 65 (FGE.65): consideration of sulfur-substituted furan derivatives used as flavouring agents evaluated by JECFA (59th meeting) structurally related to a subgroup of substances within the group of 'furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14' evaluated by EFSA in FGE.13Rev1 (2009)[7].

In its opinion, the Panel stated that, 'for the flavouring substances [FL-no: 13.160, 13.193 and 13.194] no adequate NOAEL could be identified and subsequently, no conclusion as to the safety when used at levels of intake estimated using the MSDI approach could be reached'.

Also, information on the isomeric composition / composition of mixture has not been specified for these substances.'

Thus, the Panel had reservations for these substances: data on the stereoisomeric composition / composition of the mixture has not been specified and additional toxicity data are needed.

On 23 January 2014, the European Flavour Association (EFFA) submitted the requested data.

Regarding the submitted 90-day oral (gavage) toxicity study, the applicant stipulates that, although EFSA had indicated 2,5-dimethyltetrahydro-3-furylthio acetate [FL-no: 13.194] as the 'representative substance',[8] 2-methyltetrahydrofuran-3-thiol [FL-no: 13.160] was selected by the applicant as the alternative representative substance, because of its much higher commercial relevance and because it was much more easily to procure a sufficient amount of standard material. 2,5-Dimethyltetrahydro-3-furylthio acetate [FL-no: 13.194] has a rather low commercial relevance compared to [FL-no: 13.160] and consequently, the low volume of use makes it difficult to obtain a sufficient amount of sample for testing.

In addition, the applicant draws attention to the structural similarities between the selected representative for testing and the material originally selected by EFSA:

- EFSA had selected an ester, which upon hydrolysis yield the corresponding alcohol. Thus from a metabolic point of view, both materials (ester or alcohol) will have the same fate.

[4] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34-50.

[5] Commission implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p, 1-161.

[6] Commission Regulation No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96. OJ L 180, 19.7.2000, p. 8-16.

[7] EFSA Journal 2010;8(7):1406

[8] EFSA Journal 2012;10(3):2639

- The other difference between the alternative representative substance and the substance selected by EFSA is the substitution pattern: although the selected (tested) representative substance, 2-methyltetrahydrofuran-3-thiol has only one methylgroup and the originally indicated representative substance has two methyl substituents, both molecules are structurally very similar and both substances are expected to participate in common routes of absorption, distribution, and metabolic detoxication, and exhibit similar toxicological properties.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission requests the European Food Safety Authority (EFSA) to evaluate this new information and, depending on the outcome, proceed to the full evaluation on these flavouring substances in accordance with Commission Regulation (EC) No 1565/2000.

ASSESSMENT

The approach used by EFSA for safety evaluation of flavouring substances is referred to in Commission Regulation (EC) No 1565/2000, hereafter named the 'EFSA Procedure'. This Procedure is based on the Opinion of the Scientific Committee on Food (SCF, 1999), which has been derived from the evaluation procedure developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1995; JECFA, 1996; JECFA, 1997; JECFA, 1999), hereafter named the 'JECFA Procedure'. The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (the Panel) compares the JECFA evaluation of structurally related substances with the result of a corresponding EFSA evaluation, focussing on specifications, intake estimations and toxicity data, especially genotoxicity data. The evaluations by EFSA will conclude whether the flavouring substances are of no safety concern at their estimated levels of intake, whether additional data are required or whether certain substances should not be evaluated through the EFSA Procedure.

The following issues are of special importance.

Intake

In its evaluation, the Panel as a default uses the Maximised Survey-derived Daily Intake (MSDI) approach to estimate the *per capita* intakes of the flavouring substances in Europe.

In its evaluation, the JECFA includes intake estimates based on the MSDI approach derived from both European and USA production figures. The highest of the two MSDI figures is used in the evaluation by the JECFA. It is noted that in several cases, only the MSDI figures from the USA were available, meaning that certain flavouring substances have been evaluated by the JECFA only on the basis of these figures. For Register substances for which this is the case the Panel will need EU production figures in order to finalise the evaluation.

When the Panel examined the information provided by the European Flavour Industry on the use levels in various foods, it appeared obvious that the MSDI approach in a number of cases would grossly underestimate the intake by regular consumers of products flavoured at the use level reported by the Industry, especially in those cases where the annual production values were reported to be small. In consequence, the Panel had reservations about the data on use and use levels provided and the intake estimates obtained by the MSDI approach. It is noted that the JECFA, at its 65th meeting considered 'how to improve the identification and assessment of flavouring agents, for which the MSDI estimates may be substantially lower than the dietary exposures that would be estimated from the anticipated average use levels in foods' (JECFA, 2006).

In the absence of more accurate information that would enable the Panel to make a more realistic estimate of the intakes of the flavouring substances, the Panel has decided also to perform an estimate of the daily intakes per person using a modified Theoretical Added Maximum Daily Intake (mTAMDI) approach based on the normal use levels reported by Industry.

As information on use levels for the flavouring substances has not been requested by the JECFA or has not otherwise been provided to the Panel, it is not possible to estimate the daily intakes using the mTAMDI approach for the substances evaluated by the JECFA. The Panel will need information on use levels in order to finalise the evaluation.

Threshold of 1.5 microgram/person per day (Step B5) used by the JECFA

The JECFA uses the threshold of concern of 1.5 microgram (µg)/person per day as part of the evaluation procedure:

'The Committee noted that this value was based on a risk analysis of known carcinogens which involved several conservative assumptions. The use of this value was supported by additional information on developmental toxicity, neurotoxicity and immunotoxicity. In the judgement of the

Committee, flavouring substances for which insufficient data are available for them to be evaluated using earlier steps in the Procedure, but for which the intake would not exceed 1.5 µg per person per day would not be expected to present a safety concern. The Committee recommended that the Procedure for the Safety Evaluation of Flavouring Agents used at the forty-sixth meeting be amended to include the last step on the right-hand side of the original procedure ('Do the condition of use result in an intake greater than 1.5 µg per day?')' (JECFA, 1999).

In line with the Opinion expressed by the Scientific Committee on Food (SCF, 1999), the Panel does not make use of this threshold of 1.5 µg per person per day.

Genotoxicity

As reflected in the Opinion of SCF (SCF, 1999), the Panel has in its evaluation focussed on a possible genotoxic potential of the flavouring substances or of structurally related substances. Generally, substances for which the Panel has concluded that there is an indication of genotoxic potential *in vitro,* will not be evaluated using the EFSA Procedure until further genotoxicity data are provided. Substances for which a genotoxic potential *in vivo* has been concluded, will not be evaluated through the Procedure.

Specifications

Regarding specifications, the evaluation by the Panel could lead to a different opinion than that of JECFA, since the Panel requests information on e.g. isomerism.

Structural Relationship

In the consideration of the JECFA evaluated substances, the Panel will examine the structural relationship and metabolism features of the substances within the flavouring group and compare this with the corresponding FGE.

1. History of the evaluation of the substances in the present FGE

In FGE.65, which covered a group of 33 JECFA-evaluated flavouring substances consisting of sulfur-substituted furan derivatives (JECFA, 2003), the Panel concluded that no NOAEL could be derived for the four substances [FL-no: 13.056, 13.160, 13.193 and 13.194] or for structurally related substances. Accordingly, additional toxicity data were required for these substances.

FGE	Opinion adopted	Link	No. of substances
FGE.65	25 November 2009	http://www.efsa.europa.eu/en/scdocs/scdoc/1406.htm	33
FGE.65Rev1	19 January 2015		33

The present revision of FGE.65 (FGE.65Rev1) concerns a reconsideration of three substances [FL-no: 13.160, 13.193 and 13.194], based on additional toxicity data. A 14 day palatability and range finding study followed by a 90-day dietary study, have now been provided for 2-methyltetrahydrofuran-3-thiol [FL-no: 13.160]. This substance is considered representative for [FL-no: 13.193 and 13.194]. Furthermore, for these three substances [FL-no: 13.160, 13.193 and 13.194] information on the composition of the stereoisomeric mixture has been provided.

2. Presentation of the substances in the JECFA Flavouring Group

2.1. Description

2.1.1. JECFA status

At its 59th meeting the JECFA (JECFA, 2002a) concluded the following:

'The Committee concluded that use of flavouring agents in this group of 33 thiofurfuryl and thiofuran derivatives at current levels of intake would not present a safety concern. In the Procedure, data on toxicity were required for all the evaluations. The Committee noted the absence of data on the metabolic fate of these substances but considered that their potential metabolism via the reactive divalent sulfur atom and their very low levels of use as flavouring agents were consistent with the outcome of the evaluations.'

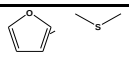
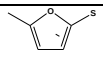
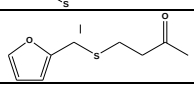
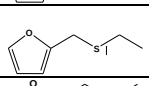
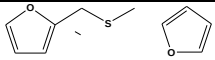
These 33 substances evaluated at the 59th JECFA meeting have been presented in Table 1.

2.1.2. EFSA considerations

The Panel concluded that all the substances in the JECFA flavouring group of sulfur-substituted furan derivatives are structurally related to a group of sulfur-containing furane derivatives evaluated within the group of 'Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14 evaluated by EFSA in the Flavouring Group Evaluation 13, Revision 2 (FGE.13Rev2; (EFSA CEF Panel, 2011).

This group of flavouring substances is very diverse with respect to their chemical structures and in acconcordance with the approach followed in FGE.13Rev2 (EFSA CEF Panel, 2011) the group has been subdivided into five subgroups (see Table 1). Because of lack of data on metabolism on candidate or supporting substances in FGE.13Rev2, the metabolism of these FGE.13 substances has been evaluated by comparison with information on the metabolism of other (non-furan) sulfur-containing substances in FGE.08Rev5 (EFSA CEF Panel, 2012). It was decided that the sulfur-containing furan candidate substances in FGE.13Rev2 could not be anticipated to be metabolised to innocuous products and therefore these substances were evaluated via the B-side of the Procedure. The same approach has been followed by the JECFA at its 59th meeting (JECFA, 2002a).

Table 1: Grouping of 33 thiofurfuryl and thiofuran derivatives evaluated by the JECFA

FL-no JECFA-no	EU Register name	Structural formula
	Ia Sulphides	
13.053 1076	Methyl furfuryl sulfide	
13.065 1062	2-Methyl-5-(methylthio)furan	
13.152 1061	2-Methyl-3-(methylthio)furan	
13.196 1084	4-[(2-Furanylmethyl)thio]-2-pentanone	
13.032 1077	Furfuryl isopropyl sulfide	
13.056 1080	Difurfuryl sulfide[9]	

[9] The Commission has communicated that this substance is in the process of being deleted from the Union List.

Table 1: Grouping of 33 thiofurfuryl and thiofuran derivatives evaluated by the JECFA

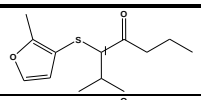
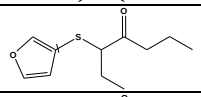
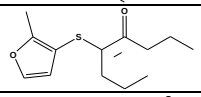
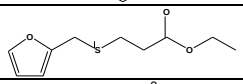
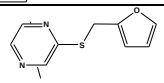
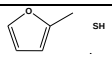
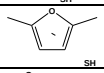
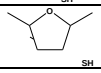
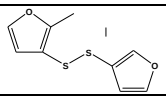
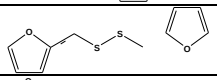
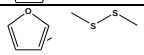
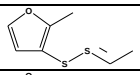
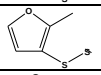
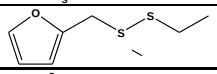
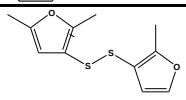
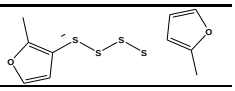
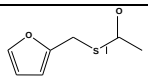
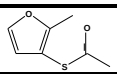
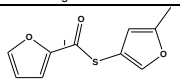
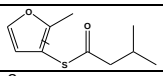
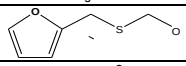
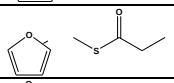
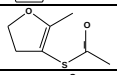
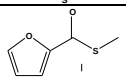
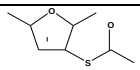
FL-no JECFA-no	EU Register name	Structural formula
13.075 1086	2,6-Dimethyl-3-((2-methyl-3-furyl)thio)heptan-4-one	
13.077 1085	3-((2-Methyl-3-furyl)thio)heptan-4-one	
13.078 1087	4-((2-Methyl-3-furyl)thio)nonan-5-one	
13.093 1088	Ethyl 3-(2-furfurylthio)propionate	
13.151 1082	2-Methyl-3,5 and 6-(furfurylthio)pyrazine	 2 or 5 or 6 -Methyl-3-(furfurylthio)pyrazine
	Ib Thiols	
13.026 1072	2-Furanmethanethiol	
13.055 1060	2-Methylfuran-3-thiol	
13.071 1063	2,5-Dimethylfuran-3-thiol	
13.160 1090	2-Methyltetrahydrofuran-3-thiol	
13.193 1091	2,5-Dimethyltetrahydro-3-furanthiol	
	Ic Disulphides	
13.016 1066	bis-(2-Methyl-3-furyl) disulfide	
13.050 1081	Difurfuryl disulfide	
13.064 1078	Methyl furfuryl disulfide	
13.082 1065	Propyl 2-methyl-3-furyl disulfide	
13.079 1064	Methyl 2-methyl-3-furyl disulfide	
13.197 1079	Furfuryl propyl disulfide	
13.015 1067	bis-(2,5-Dimethyl-3-furyl) disulfide	
	Id Polysulphides	
13.017 1068	bis-(2-Methyl-3-furyl) tetrasulfide	
	Ie Thioester	
13.033 1074	*S*-Furfuryl acetothioate	

Table 1: Grouping of 33 thiofurfuryl and thiofuran derivatives evaluated by the JECFA

FL-no JECFA-no	EU Register name	Structural formula
13.153 1069	2-Methyl-3-furyl thioacetate	
13.040 1071	*S*-2,5-Dimethyl-3-thiofuroylfuran	
13.041 1070	2,5-Dimethyl-3-(isovalerylthio)furan	
13.051 1073	*S*-Furfuryl thioformate	
13.063 1075	*S*-Furfuryl propanethioate	
13.086 1089	4,5-Dihydro-2-methyl-3-thioacetoxyfuran	
13.142 1083	*S*-Methyl 2-furanthiocarboxylate	
13.194 1092	2,5-Dimethyltetrahydro-3-furyl thio acetate	

2.2. Isomers

2.2.1. Status

The following substances [FL-no: 13.075, 13.077, 13.078, 13.160, 13.193, 13.194 and 13.196] in the group of the JECFA-evaluated sulfur substituted furan derivatives have one or more chiral centres.

2.2.2. EFSA considerations

For the seven substances, listed in Section 2.2.1, the configurations of the chiral centres have been specified and information is available on the compositions of the stereoisomeric mixtures.

2.3. Specifications

2.3.1. Status

The JECFA specifications are available for all 33 substances (JECFA, 2002b). See Table 2.

2.3.2. EFSA considerations

The available specifications are considered adequate for all 33 substances (see Section 2.2).

3. Intake estimation

3.1. Status

For all 33 substances evaluated through the JECFA Procedure production volumes, based on which MSDI values can be calculated, are available for the EU, see Table 4.

SUMMARY OF SPECIFICATION DATA

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

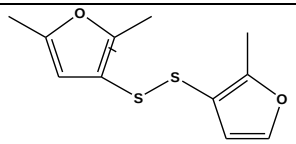
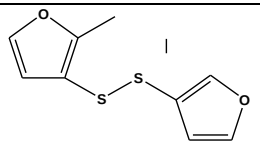
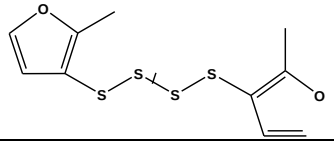
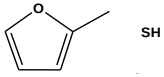
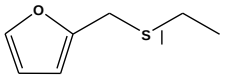
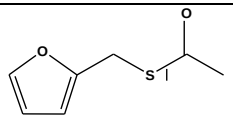
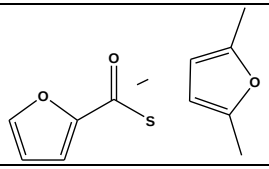
FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[(a)] Solubility in ethanol[(b)]	Boiling point, °C[(c)] Melting point, °C ID test Assay minimum	Refrac. Index[(d)] Spec.gravity[(e)]	EFSA comments
13.015 1067	bis-(2,5-Dimethyl-3-furyl) disulfide		3476 722 28588-73-0	Liquid $C_{12}H_{14}O_2S_2$ 254.38	Insoluble Miscible	110-111 (1 hPa) IR NMR 99 %	1.548-1.568 1.140-1.152	
13.016 1066	bis-(2-Methyl-3-furyl) disulfide		3259 723 28588-75-2	Liquid $C_{10}H_{10}O_2S_2$ 226.31	Insoluble Miscible	84-85 (0.4 hPa) NMR 98 %	1.572-1.583 1.146-1.154	
13.017 1068	bis-(2-Methyl-3-furyl) tetrasulfide		3260 724 28588-76-3	Liquid $C_{10}H_{10}O_2S_4$ 290.43	Insoluble Slightly soluble	142-147 (1 hPa) NMR 96 %	1.671-1.693 1.366-1.378	
13.026 1072	2-Furanmethanethiol		2493 2202 98-02-2	Liquid C_5H_6OS 114.16	Insoluble Miscible	154-155 NMR 97 %	1.527-1.542 1.125-1.135 (20°)	
13.032 1077	Furfuryl isopropyl sulfide		3161 2248 1883-78-9	Liquid $C_8H_{12}OS$ 156.24	Insoluble Miscible	84 (21 hPa) NMR 97 %	1.497-1.508 1.013-1.020 (20°)	
13.033 1074	*S*-Furfuryl acetothioate		3162 2250 13678-68-7	Liquid $C_7H_8O_2S$ 156.20	Insoluble Miscible	90-92 (16 hPa) NMR 95 %	1.522-1.529 1.149-1.155 (20°)	
13.040 1071	(*S*)-2,5-Dimethyl-3-thiofuroylfuran		3481 2323 65505-16-0	Liquid $C_{11}H_{10}O_3S$ 222.26	Insoluble Miscible	79-83 (0.9 hPa) IR NMR 98 %	1.512-1.519 1.047-1.058	

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

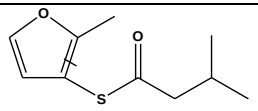
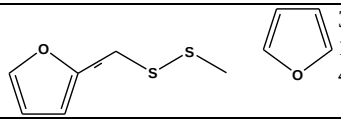
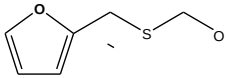
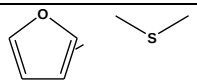
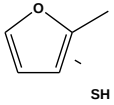
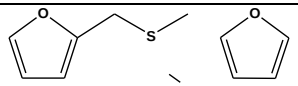
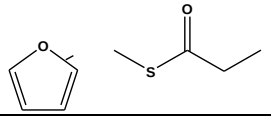
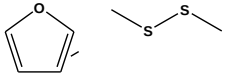
FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[a] Solubility in ethanol[b]	Boiling point, °C[c] Melting point, °C ID test Assay minimum	Refrac. Index[d] Spec.gravity[e]	EFSA comments
13.041 1070	2,5-Dimethyl-3-(isopentylthio)furan		3482 2324 55764-28-8	Liquid $C_{11}H_{16}O_2S$ 212.31	Insoluble Miscible	124-125 (8 hPa) IR NMR 99 %	1.492-1.508 1.025-1.034	Registername to be changed to 2,5-dimethyl-3-(isovalerylthio)furan.
13.050 1081	Difurfuryl disulfide		3146 11480 4437-20-1	Liquid $C_{10}H_{10}O_2S_2$ 226.31	Slightly soluble Miscible	229-230 NMR 96 %	1.585-1.598 1.229-1.248	
13.051 1073	*S*-Furfuryl thioformate		3158 11770 59020-90-5	Liquid $C_6H_6O_2S$ 142.17	Insoluble Miscible	80-87 (13 hPa) NMR 97 %	1.539-1.549 1.213-1.223 (20°)	
13.053 1076	Methyl furfuryl sulfide		3160 11482 1438-91-1	Liquid C_6H_8OS 128.19	Insoluble Miscible	62-63 (36 hPa) NMR 97 %	1.518-1.530 1.082-1.089 (20°)	
13.055 1060	2-Methylfuran-3-thiol		3188 11678 28588-74-1	Liquid C_5H_6OS 114.16	Insoluble Miscible	57-60 (57 hPa) NMR 95 %	1.509-1.530 1.141-1.150	According to JECFA: Min. assay value is '95' and secondary components 'Bis(2-methyl-3-furyl)disulfide'.
13.056 1080	Difurfuryl sulfide		3238 11438 13678-67-6	Liquid $C_{10}H_{10}O_2S$ 194.25	Insoluble Miscible	135-143 (18hPa) NMR 95 %	1.545-1.560 1.144-1.154	
13.063 1075	*S*-Furfuryl propanethioate		3347 11484 59020-85-8	Liquid $C_8H_{10}O_2S$ 170.23	Insoluble Miscible	95-97 (13 hPa) NMR 97 %	1.506-1.521 1.089-1.111 (20°)	
13.064 1078	Methyl furfuryl disulfide		3362 11513 57500-00-2	Liquid $C_6H_8OS_2$ 160.25	Insoluble Miscible	102-103.5(30hPa NMR 95 %	1.565-1.573 1.177-1.184 (20°)	

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

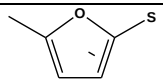
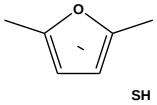
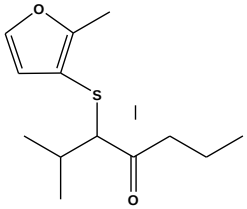
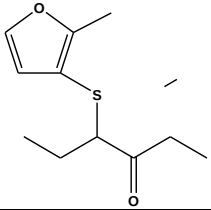
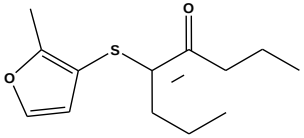
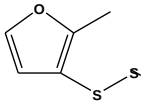
FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[a] Solubility in ethanol[b]	Boiling point, °C[c] Melting point, °C ID test Assay minimum	Refrac. Index[d] Spec.gravity[e]	EFSA comments
13.065 1062	2-Methyl-5-(methylthio)furan		3366 11550 13678-59-6	Liquid C_6H_8OS 128.19	Insoluble Miscible	66-67 (30 hPa) NMR 98 %	1.514-1.520 1.055-1.059 (20°)	
13.071 1063	2,5-Dimethylfuran-3-thiol		3451 11457 55764-23-3	Liquid C_6H_8OS 128.19	Insoluble Miscible	70 (39 hPa) IR 98 %	1.500-1.520 1.138-1.144	
13.075 1086	2,6-Dimethyl-3-((2-methyl-3-furyl)thio)heptan-4-one		3538 11915 61295-51-0	Liquid $C_{14}H_{22}O_2S$ 254.39	Insoluble Miscible	90-92 (0.3 hPa) IR NMR 94 %	1.488-1.494 1.006.1.022	Racemate (EFFA, 2010a). According to JECFA: Min. Assay value is '94' and secondary components '2,6-Dimethyl-2-[(2-methyl-3-furyl)thio]-4-heptanone'.
13.077 1085	3-((2-Methyl-3-furyl)thio)heptan-4-one		3570 11922 61295-41-8	Liquid $C_{12}H_{18}O_2S$ 226.33	Insoluble Miscible	85-86 (0.4 hPa) IR NMR 97 %	1.496-1.502 1.041-1.045	Racemate (EFFA, 2010a).
13.078 1087	4-((2-Methyl-3-furyl)thio)nonan-5-one		3571 11923 61295-50-9	Liquid $C_{14}H_{22}O_2S$ 254.39	Insoluble Miscible	102-103(0.3hPa) IR NMR 98 %	1.489-1.496 1.000-1.012	Racemate (EFFA, 2010a).
13.079 1064	Methyl 2-methyl-3-furyl disulfide		3573 11924 65505-17-1	Liquid $C_6H_8OS_2$ 160.25	Insoluble Miscible	72.5-75 (7 hPa) IR NMR 97 %	1.558-1.563 1.203-1.208	According to JECFA: Min. assay value is '97' and secondary components 'up to 3% bis(2-methyl-3-furyl)disulfide'.

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

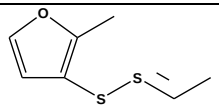
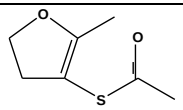
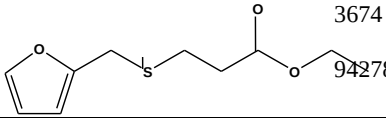
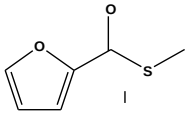
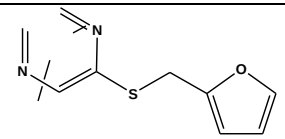
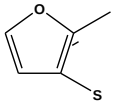
FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[a] Solubility in ethanol[b]	Boiling point, °C[c] Melting point, °C ID test Assay minimum	Refrac. Index[d] Spec.gravity[e]	EFSA comments
13.082 1065	Propyl 2-methyl-3-furyl disulfide		3607 61197-09-9	Liquid $C_8H_{12}OS_2$ 188.32	Insoluble Miscible	75.5-79 (2 hPa) IR NMR 97 %	1.534-1.539 1.094-1.104	According to JECFA: Min. assay value is '97' and secondary components 'up to 2% bis(2-methyl-3-furyl)disulfide and propyl disulfide'.
13.086 1089	4,5-Dihydro-2-methyl-3-thioacetoxyfuran		3636 26486-14-6	Liquid $C_7H_{10}O_2S$ 158.22	Miscible	40-42 (0.1 hPa) NMR 99 %	1.517-1.521 1.132-1.139	
13.093 1088	Ethyl 3-(2-furfurylthio)propionate		3674 94278-27-0	Liquid $C_{10}H_{14}O_3S$ 214.28	Insoluble Miscible	244 (975 hPa) IR NMR 97 %	1.500-1.509 1.121-1.138	
13.142 1083	*S*-Methyl 2-furanthiocarboxylate		3311 11547 13679-61-3	Liquid $C_6H_6O_2S$ 142.17	Insoluble Miscible	92-93 (14 hPa) NMR 97 %	1.567-1.573 1.230-1.241	
13.151 1082	2-Methyl-3,5 and 6-(furfurylthio)pyrazine	 2 or 5 or 6 -Methyl-3-(furfurylthio)pyrazine	3189 2287 65530-53-2	Liquid $C_{10}H_{10}ON_2S$ 206.26	Insoluble Miscible	85-87 (13 hPa) NMR 99 %	1.580-1.586 1.138-1.148 (20°)	According to JECFA: Min. assay value is '99' and 'Mixture of isomers: 70% 2,3-; 29% 2,6-; trace 2,5-'.
13.152 1061	2-Methyl-3-(methylthio)furan		3949 63012-97-5	Liquid C_6H_8OS 128.19	Insoluble Miscible	172 NMR 95 %	1.506-1.514 1.064-1.071 (20°)	

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

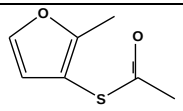
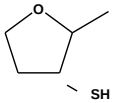
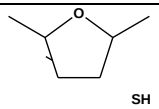
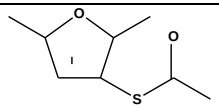
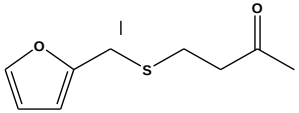
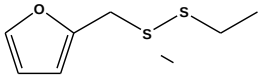
FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[a] Solubility in ethanol[b]	Boiling point, °C[c] Melting point, °C ID test Assay minimum	Refrac. Index[d] Spec.gravity[e]	EFSA comments
13.153 1069	2-Methyl-3-furyl thioacetate		 55764-25-5	Liquid $C_7H_8O_2S$ 156.2	Insoluble Miscible	222-224 NMR 92 %	1.444-1.451 1.140-1.159	2-Ethanethoic acid, *S*-(2-methyl-3-furanyl) ester (92%), secondary components (*Z*)- and (*E*)-2-Methyl-3-tetrahydrofuranthiol acetate (sum > 95%), (EFFA, 2010a).
13.160 1090	2-Methyltetrahydrofuran-3-thiol		3787 57124-87-5	Liquid $C_5H_{10}OS$ 118.2	Insoluble Miscible	79 (70 hPa) IR NMR MS 97 %	1.475-1.491 1.042-1.049	Mixtur of diastereoisomers (EFFA, 2010a). According to JECFA: Min. Assay value is '97' and '71 % *trans* and 26 % *cis* isomer'.
13.193 1091	2,5-Dimethyltetrahydro-3-furanthiol		3971 26486-21-5	Liquid $C_6H_{12}OS$ 132.2	Insoluble Miscible	175 IR NMR MS 96 %	1.477-1.484 1.040-1.048 (20°)	Mixture of stereoisomers: 40-50% 2*S*,3*R*,5*R*: 25-30% 2*R*,3*S*,5*S*: 15-20% 2*R*,3*R*,5*S*: 5-10% 2*S*,3*S*,5*R*: others <5% (EFFA, 2015). According to JECFA: Min. Assay value is '96 (mixture of 4 stereoisomers)'. Composition of stereoisomeric mixture to be specified.

Table 2: Specification Summary of the Substances in the JECFA Flavouring Group (JECFA, 2002b)

FL-no JECFA -no	EU Register name	Structural formula	FEMA no CoE no CAS no	Phys.form Mol.formula Mol.weight	Solubility[(a)] Solubility in ethanol[(b)]	Boiling point, °C[(c)] Melting point, °C ID test Assay minimum	Refrac. Index[(d)] Spec.gravity[(e)]	EFSA comments
13.194 1092	2,5-Dimethyltetrahydro-3-furyl thio acetate		3972 252736-39-3	Liquid $C_8H_{14}O_2S$ 174.3	Insoluble Miscible	50 (1 hPa) IR NMR MS 90 %	1.468-1.474 0.933-1.003 (20°)	Mixture of stereoisomers: 35-45% 2*S*,3*R*,5*R*: 25-30% 2*R*,3*S*,5*S*: 10-15% 2*R*,3*R*,5*S*: 5-10% 2*S*,3*S*,5*R*; others <5% (EFFA, 2015). According to JECFA: Min. Assay value is '90 (mixture of 4 stereoisomers)' and secondary components '2,5-dimethyltetrahydrofuran-3-thiol & dimethyltetrahydro-3-furyl dithioacetate'.
13.196 1084	4-[(2-Furanylmethyl)thio]-2-pentanone		3840 180031-78-1	Liquid $C_{10}H_{14}O_2S$ 198.29	Insoluble 50% Soluble in ethanol	113 IR MS 97 %	1.513-1.518 1.088-1.096	Racemate (EFFA, 2010a).
13.197 1079	Furyl propyl disulfide		3979 252736-36-0	Liquid $C_8H_{12}OS_2$ 188.29	Insoluble Miscible	121-123 (23hPa) MS 96 %	1.539-1.547 1.103-1.113 (20°)	

(a): Solubility in water, if not otherwise stated.
(b): Solubility in 95 % ethanol, if not otherwise stated.
(c): At 1013.25 hPa, if not otherwise stated.
(d): At 20°C, if not otherwise stated.
(e): At 25°C, if not otherwise stated.

4. Genotoxicity data

4.1. Genotoxicity studies – Text taken[10] from the JECFA (JECFA, 2003)

No data on genotoxicity were available for the JECFA-evaluated substances.

4.2. Genotoxicity studies – Text taken[11] from EFSA FGE.13Rev2 (EFSA CEF Panel, 2011)

In vitro /in vivo

No genotoxicity data were available on any of the 14 sulfur-containing candidate substances in main group II of FGE.13Rev2, nor on their related supporting substances. The lack of data does not allow to conclude on their potential for genotoxicity. By default, these 14 substances in main group II can be evaluated through the Procedure.

4.3. EFSA considerations

There are no genotoxicity data on candidate or supporting substances in this FGE. Therefore the genotoxicity of these substances cannot be properly assessed. However, this would not preclude the evaluation of the substances through the Procedure.

5. New toxicity data considered by the Panel in FGE.65Rev1

5.1. 14- and 90-day dietary study with 2-methyltetrahydrofuran-3-thiol [FL-no: 13.160]

14-day study

A 14-day palatability and dose-range finding study was performed with the candidate substance 2-methyltetrahydrofuran-3-thiol [FL-no:13.160] (Kappeler, 2013). Four groups of adult Crl:CD(SD) rats (3/sex/group) were placed into one control and three test groups. The dietary concentrations of methyltetrahydrofuran-3-thiol were adjusted to obtain provisional consumptions of 0, 75, 500 and 1000 mg/kg bw per day. A NOAEL of 75 mg/kg bw per day was identified, based on a body weight gain reduction in males at dose levels of 500 and 1000 mg/kg bw per day, mostly attributable to reduced feed intake. In the females, the difference in body weight gain did not reach statistical significance (N=3/sex/group).

90-day study

Based on the results from the 14-day study, the test substance, 2-methyltetrahydrofuran-3-thiol (purity 97.27 %) was administered to Crl:CD(SD) rats (10/sex/dose) by gavage at doses of 0, 5, 55 and 125 mg in corn oil/kg bw per day (Kappeler, 2014). The 90-day study has been conducted in accordance with the OECD Test Guideline 408 and GLP principles. In this study, the animals of the control group received vehicle only (corn oil). All animals were subject to daily clinical examinations and twice daily observed for observations for mortality and morbidity. Detailed physical examinations, including body weight and food consumption measurements were carried out once per week. Ophthalmic examinations were performed before the start of the study and in week 12. Clinical pathology parameters (haematology, coagulation, serum chemistry and urinalysis) were evaluated for all animals at the scheduled necropsy, after 90 days of treatment. Blood for haematology and serum chemistry was collected at necropsy after overnight fast and urine was collected overnight prior to necropsy. Coagulation was measured in blood collected from anesthetized animals prior to sacrifice. Selected organs were weighed at the time of necropsy and selected tissues were examined microscopically. All tissues were examined microscopically for animals of the 125 mg/kg bw per day groups. In addition,

[10] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed.

[11] The text is taken verbatum from the indicated reference source, but text related to subgroups not included in the present FGE has been removed.

all tissues showing pathological changes that might be attributable to the testing substance in the top dose group were also examined for all animals of the two lower intake level groups.

All but one male and one female animal of the high dose group survived to the end of the study and were subjected to complete necropsy. The high-dose male was euthanized in extremis following fractures of nasal bone and hard palate with subsequent inflammations; the cause of death for the high-dose female was not completely clear, but may have been related to a gavage accident. Neither of the two deaths was considered to be treatment-related.

No differences between treated and control groups were noted in clinical or ophthalmic observations or urinalysis. Statistically significant lower final mean body weight (18 %) was reported in males of the 125 mg/kg bw per day group and correlated with slightly reduced feed consumption in this group. Slightly lower cumulative body weight was also noted in males of the 55 mg/kg bw per day group (up to 3.6 %) throughout the study and in females of the 125 mg/kg bw per day groups (5 %) toward the end of the study.

In haematology, lower mean red blood cell counts (-5% to -23%), hemoglobin (-3% to -16%), and hematocrit (-2% to -12%) and higher mean values for relative (40% to 243%) and absolute reticulocyte counts (31% to 155%) at ≥ 55 mg/kg per day were observed in both sexes. Lower mean values for mean corpuscular hemoglobin concentration (MCHC) and higher mean values for mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), hemoglobin distribution width (HDW; females only) were present in males and females at 125 mg/kg per day. This pattern of changes is consistent with regenerative anemia and correlates with hypercellularity of the bone marrow. Higher mean platelet counts (23%) were also noted in males at 125 mg/kg per day. The observations in haematology at the top dose correlate with increased spleen weight at the same dose and macroscopic and microscopic findings in the spleen (brown pigmentation) indicative of anaemia and compensatory extramedullary haematopoiesis in both sexes and with hypercellularity in the bone marrow, starting at 55 mg/kg bw per day and up in males and at 125 mg/kg bw per day in females. Macroscopic findings in the spleen were characterized as dark red discoloration at 55 mg/kg bw per day (1/10 female) and 125 mg/kg bw per day (4/10 males).

Clinical chemistry analysis revealed higher serum bilirubin, phosphorus levels that were statistically significant at the top dose for both sexes with a trend from 5 mg/kg bw per day in males and 55 mg/kg bw per day in females. Additional increases that were not statistically significant were noted for glucose concentrations and higher enzyme activities for alkaline phosphatase (ALP), and/or sorbitol dehydrogenase in males and/or females. Lower triglyceride concentration was noted in the 125 mg/kg bw per day group males and females. The changes in bilirubin, phosphorus and ALP are consistent with spleen and liver pigmentation and indicate extravascular haemolysis.

Lower thymus weight and atrophy in males at the top dose was attributed to lower body weight in that group. In addition to spleen and bone marrow findings, other microscopic findings included thymus atrophy in males, brown pigmentation of the liver Kupffer cells in both sexes and paraganglion hyperplasia in the periaortic soft tissue (one female) at 125 mg/kg bw per day; degeneration of the olfactory epithelium in the nasal levels II, III, and IV for both sexes at 55 mg/kg bw per day and above; and hyaline droplets in the proximal tubules of the kidneys in males, but not females, starting at 5 mg/kg bw per day and granular casts noted at 55 mg/kg bw per day and above. Higher kidney weights were noted in males only, starting at the 55 mg/kg bw per day and they correlated with the presence of hyaline droplets and/or granular casts and is typical of hyaline droplet nephropathy characteristic of male rats. Minimal chronic progressive nephropathy was observed in high incidence (7/10 animals) in the control group and in the low-dose group (8/10). Both incidence and severity increased in the mid- and high-dose groups (up to 100 % affected, but severity not more than 20 % ‘mild’ in the high-dose group). According to the study report, these renal changes in the males are not observed in the female animals and not relevant for other species, including humans (see also Hard et al., 1993; Hard and Khan, 2004; Hard, 2008).

It was concluded that oral exposure to 2-methyltetrahydrofuran-3-thiol resulted in no adverse effects in the 5 mg/kg bw per day group of females. In males, findings in the kidneys were noted at this dose. However, such observations are commonly seen in male rats and the Panel did not consider these to be relevant to humans (Hard and Kahn, 2004; Hard, 2008). Treatment-related effects in males and females noted at 55 mg/kg bw per day and above consisted of decreased body weight, olfactory epithelium degeneration and changes in haematological parameters and findings in the spleen, liver and bone marrow consistent with increased extramedullary haematopoiesis with associated extravascular haemolysis. Therefore, the NOAEL of 2-methyltetrahydrofuran-3-thiol was 5 mg/kg bw per day for male and female Crl:CD (SD) rats, exposed to 2-methyltetrahydrofuran-3-thiol for 90 days.

A summary of the results of the 14-day and 90-day studies are shown in Table 3.

6. Application of the procedure

6.1. Application of the procedure to 33 sulfur-substituted furan derivatives by the JECFA[12] (JECFA, 2003)

According to the JECFA 18 of the substances belong to structural class II and 15 to structural class III using the decision tree approach presented by Cramer *et al.* (Cramer et al., 1978).

'None of the flavouring agents in this group was predicted to be metabolised to innocuous products. The evaluation of these agents therefore proceeded down the B (right-hand) side of the decision tree.

Step B3: The current estimated daily per capita intakes of each of the 33 flavouring agents in this group is below the threshold for human intake for the respective structural classes (540 mg per day for structural class II and 90 mg per day for structural class III). Accordingly, the evaluation of all 33 substances in the group proceeded to step B4.

Step B4: The NOEL for 2-methyl-3-furanthiol (FL-no: 13.055, JECFA no: 1060) in a 90-day dietary study in rats was 5 mg/kg bw per day (Oser, 1970b). This NOEL is appropriate for ethanoic acid, S-(2-methyl-3-furanyl) ester (FL-no: 13.153, JECFA no: 1069) because the acetate ester would be hydrolysed to 2-methyl-3-furanthiol (FL-no: 13.055, JECFA no: 1060). This NOEL is also appropriate for the closely structurally related agent, 2,5-dimethyl-3-furanthiol (FL-no: 13.071, JECFA no: 1063).

The NOEL for furfuryl isopropyl sulfide (FL-no: 13.032, JECFA no: 1077) in a 90-day dietary study in rats was 1.3 mg/kg bw per day (Posternak et al., 1969). This NOEL is also appropriate for three structurally related sulfides, 2-methyl-3-(methylthio)furan (FL-no: 13.152, JECFA no: 1061), 2-methyl-5-(methylthio)furan (FL-no: 13.065, JECFA no: 1062) and furfuryl methyl sulfide (FL-no: 13.053, JECFA no: 1076), which would be expected to participate in the same metabolic pathways as furfuryl isopropyl sulfide.

The NOEL for methyl 2-methyl-3-furyl disulfide (FL-no: 13.079, JECFA no: 1064) in a 90-day dietary study in rats was 1.2 mg/kg bw per day (Gallo et al., 1976a). This NOEL is also appropriate for three structurally related disulfides, propyl 2-methyl-3-furyl disulfide (FL-no: 13.082, JECFA no: 1065), methyl furfuryl disulfide (FL-no: 13.064, JECFA no: 1078) and furfuryl propyl disulfide (FL-no: 13.197, JECFA no: 1079).

The NOEL for bis(2-methyl-3-furyl) disulfide (FL-no: 13.016, JECFA no: 1066) in a 90-day dietary study in rats was 0.45 mg/kg bw per day (Morgareidge and Oser, 1970a). This NOEL is also appropriate for a structurally related bis-disulfide, bis(2,5-dimethyl-3-furyl) disulfide (FL-no: 13.015, JECFA no: 1067).

[12] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed

The NOEL for furfuryl mercaptan (FL-no: 13.026, JECFA no: 1072) in a multiple-dose, 13-week study in rats treated by gavage was 3 mg/kg bw per day (Phillips et al., 1977); and the NOEL for furfuryl thioacetate (FL-no: 13.033, JECFA no: 1074) in a 90-day dietary study in rats was 0.83 mg/kg bw per day (Posternak et al., 1969). These NOELs are also appropriate for the esters furfuryl thioformate (FL-no: 13.051, JECFA no: 1073) and furfuryl thiopropionate (FL-no: 13.063, JECFA no: 1075), because they are either close structural relatives of furfuryl thioacetate (FL-no: 13.033, JECFA no: 1074) or are expected to be hydrolysed to furfuryl mercaptan (FL-no: 13.026, JECFA no: 1072). The NOEL of 3 mg/kg bw per day for furfuryl mercaptan (FL-no: 13.026, JECFA no: 1072) is also appropriate for 2,2'-(dithiodimethylene) difuran (FL-no: 13.050, JECFA no: 1081), because this chemical is anticipated to be readily reduced to furfuryl mercaptan.

The NOEL for 2,5-dimethyl-3-thiofuroyl furan (FL-no: 13.040, JECFA no: 1071) in a 90-day dietary study in rats was 0.74 mg/kg bw per day (Morgareidge et al., 1974b). This NOEL is appropriate for methyl thiofuroate (FL-no: 13.142, JECFA no: 1083), because both 2,5-dimethyl-3-thiofuroyl furan and methyl thiofuroate would be hydrolysed to furoic acid.

The NOEL for 3-[(2-methyl-3-furyl)thio]-4-heptanone (FL-no: 13.077, JECFA no: 1085) in a 90- day dietary study in rats was 3.8 mg/kg bw per day (Gallo et al., 1976b). This NOEL is also appropriate for three structurally related thioketones, 4-[(2-methyl-3-furyl)thio]-2-pentanone (FL-no: 13.196, JECFA no: 1084), 2,6-dimethyl-3-[(2-methyl-3-furyl)thio]-4-heptanone (FL-no: 13.075, JECFA no: 1086) and 4-[(2-methyl-3-furyl)thio]-5-nonanone (FL-no: 13.078, JECFA no: 1087).

The NOEL for 2,2'-(thiodimethylene) difuran (FL-no: 13.056, JECFA no: 1080) in a 14-day study in rats treated in the diet was 10 mg/kg bw per day (Gill and Van Miller, 1987); that for bis(2-methyl-3-furyl) tetrasulfide (FL-no: 13.017, JECFA no: 1068) in a 90-day study was 0.56 mg/kg bw per day (Morgareidge and Oser, 1970b); that for 2,5-dimethyl-3-furan thioisovalerate (FL-no: 13.041, JECFA no: 1070) in a 90-day study was 0.73 mg/kg bw per day (Morgareidge et al., 1974a); that for 2-methyl-3-, 5- or 6-(furfurylthio)pyrazine (FL-no: 13.151, JECFA no: 1082) in a 90-day study was 1.7 mg/kg bw per day (Posternak et al., 1975); and that for ethyl 3-(furfurylthio)propionate (FL-no: 13.093, JECFA no: 1088) in a 90-day study was 17 mg/kg bw per day (Bio-Research Laboratory, 1980).

The NOEL for 2-methylthioacetoxy-4,5-dihydrofuran (FL-no: 13.086, JECFA no: 1089) in a 1-year dietary study in rats was 8.3 mg/kg bw per day (Munday and Gellatly, 1974). This NOEL is also appropriate for three structurally related analogues, 2-methyl-3-tetrahydrofuranthiol (FL-no: 13.160, JECFA no: 1090), *cis*- and *trans*-2,5-dimethyl-3-tetrahydrofuranthiol (FL-no: 13.193, JECFA no: 1091) and *cis*-and *trans*-2,5-dimethyltetrahydro-3-furyl thioacetate (FL-no: 13.194, JECFA no: 1092), because these chemicals are expected to be hydrolysed to the corresponding dihydro- or tetrahydrofuranthiol.

The stepwise evaluations of the 33 substances evaluated by the JECFA are summarised in Table 4.

6.2. Application of the procedure to 27 furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms by EFSA[13] in FGE.13Rev2 (EFSA CEF Panel, 2011)

Only the text relevant for FGE.65Rev1 has been included here. Where necessary some editorial changes were included to maintain legibility and numbers of substances evaluated in FGE.13Rev2 refer only to the number of sulfur-containing furan derivatives (i.e. 14 from main group II out of the 25 substances considered in FGE.13Rev2).

For the safety evaluation of the sulfur-containing candidate substances the Procedure as outlined in Appendix A was applied. The stepwise evaluations of the 14 substances of main group II of FGE13Rev2 are summarised in Table 5.

[13] The text is taken verbatim from the indicated reference source, but text related to substances not included in the present FGE has been removed

Step 1

One of these 14 sulfur-containing candidate substances evaluated via the Procedure are classified into structural class II and 13 are classified into structural class III according to the decision tree approach by Cramer et al. (Cramer et al., 1978) (see Table 2a of FGE.13Rev2).

Step 2

Taking into account the metabolic pathways described in Section 4, none of the candidate substances are predicted to be metabolised to innocuous products. Therefore, the evaluation of the 14 sulfur-containing candidate substances proceeds *via* the B-side of the evaluation scheme.

Step B3

The one candidate substance [FL-no: 13.145], which has been assigned to structural class II, has an estimated European daily *per capita* intakes (MSDI) of 0.0024 µg (Table 2a of FGE.13Rev2). This intake is below the threshold of concern of 540 µg/person per day for structural class II. The estimated daily *per capita* intakes of the 13 candidate substances assigned to structural class III range from 0.0012 to 37 µg, which is also below the threshold of concern for the structural class of 90 µg/person per day. Therefore, the safety evaluation proceeds to step B4 for all 14 candidate substances.

Step B4

Since no toxicity data are available on the sulfur-containing candidate substances in main group II of FGE.13Rev1, the relevant NOAEL values originate from structurally related supporting substances.

Subgroup IIa sulphides [FL-no: 13.114, 13.124, 13.141, 13.143, 13.145 and 13.199]:

The candidate substances ethyl furfuryl sulfide [FL-no: 13.124], methyl 5-methylfurfuryl sulfide [FL-no: 13.145] and 2,5-dimethyl-3-(methylthio)furan [FL-no: 13.114] are expected to participate in the same metabolic pathways as the supporting substance furfuryl isopropyl sulfide [FL-no: 13.032] and therefore to have same toxicological properties. No effects were observed for furfuryl isopropyl sulfide in a 90-day dietary study with rats at a single dose level (1.34 mg/kg bw per day) (Posternak et al., 1969). Comparison of the only level tested with no effect taken as a NOAEL with the estimated daily *per capita* intakes based on the MSDI approach and expressed in µg/kg bw per day for ethyl furfuryl sulfide [FL-no: 13.124], methyl 5-methylfurfuryl sulfide [FL-no: 13.145] and 2,5-dimethyl-3-(methylthio)furan [FL-no: 13.114] provides adequate margins of safety > 10^5.

After ester hydrolysis, the candidate substances methyl (2-furfurylthio)acetate and methyl 3-furfurylthio) propionate [FL-no: 13.141 and 13.143] are anticipated to be metabolised and to have toxicological properties similar to the supporting substance ethyl-3-(2-furfurylthio) propionate [FL-no: 13.093]. For this substance an NOAEL of 5.78 mg/kg bw per day has been identified in a 90-day study (Bio-Research Laboratory, 1980). Comparison of this NOAEL with the estimated daily *per capita* intakes based on the MSDI approach and expressed in µg/kg bw per day of methyl (2-furfurylthio)acetate and methyl 3-furfurylthio) propionate [FL-no: 13.141 and 13.143] provides an adequate margin of safety of 3.2×10^7 for both substances.

Candidate substance 3-[(2-methyl-3-furyl)thio]-butanal [FL-no: 13.199] may be evaluated by comparison of its exposure with the NOAEL from supporting substance 3-[(2-methyl-3-furyl)thio]-4-heptanone [FL-no: 13.077]. 3-[(2-Methyl-3-furyl)thio]-4-heptanone was tested in rats at a single dose level of 3.76 mg/kg bw per day in the diet for 90 days without treatment-related effects (Gallo et al., 1976b). Comparison of the estimated daily *per capita* intakes based on the MSDI approach for 3-[(2-methyl-3-furyl)thio]-butanal [FL-no: 13.199] with the NOAEL of 3.76 mg/kg bw per day for the supporting substance provided an adequate margin of safety of 1.9×10^5.

Subgroup IIb thiols [FL-no: 13.108 and 13.149]:

The candidate substance 5-methyl-2-furanmethanethiol [FL-no: 13.149] is structurally related to the supporting substance 2-furanmethanethiol [FL-no: 13.026]. The NOAEL of 2-furanmethanethiol in a multiple dose level 91-day oral gavage study with rats was 3 mg/kg bw per day (Phillips et al., 1977). Comparison of the NOAEL for 2-furanmethanethiol with the estimated daily *per capita* intake based on the MSDI approach expressed in µg/kg bw per day of 5-methyl-2-furanmethanethiol [FL-no: 13.149] provides an adequate margin of safety of 4.9×10^5.

The candidate substance 4,5-dihydro-3-mercapto-2-methylfuran [FL-no: 13.108] is structurally related to the supporting substance 2-methyl-3-thioacetoxy-4,5-dihydrofuran [FL-no: 13.086] from subgroup IIe. Several subchronic studies have been carried out with this supporting substance. A NOAEL of 1.4 mg/kg bw per day has been derived in a multiple dose level 13 weeks dietary study with rats (Munday and Gellatly, 1973). Comparison of the NOAEL for 2-methyl-3-thioacetoxy-4,5-dihydrofuran with the estimated daily *per capita* intake based on the MSDI approach expressed in µg/kg bw per day of 4,5-dihydro-3-mercapto-2-methylfuran [FL-no: 13.108] provided an adequate margin of safety of 2.3×10^3.

Subgroup IIc disulphides [FL-no: 13.113, 13.144, 13.178 and 13.185]:

In the previous version of this FGE, the candidate substance 2,5-dimethyl-3-(methyldithio)furan [FL-no: 13.113] was evaluated against a NOAEL which turned out to belong to a structurally unrelated substance. Therefore this evaluation was not valid and thus substance [FL-no: 13.113] had to be reconsidered. It may be anticipated that this disulphide will be subject to fission of the disulphide bridge. The resulting furan-containing fragment, which is more reactive than the disulphide itself, could be evaluated by comparison with the toxicity of 2-methyl-3-furanthiol [FL-no: 13.055] from subgroup IIb. The NOAEL of 2-methyl-3-furanthiol in a multiple dose level 90-day oral gavage study with rats was 5 mg/kg bw per day (Oser, 1970b). When the NOAEL for 2-methyl-3-furanthiol is compared with the estimated daily *per capita* intake based on the MSDI approach expressed in µg/kg bw per day for 2,5-dimethyl-3-(methyldithio)furan [FL-no: 13.113] an adequate margin of safety of 25×10^7 can be calculated.

For the candidate substances methyl 5-methylfurfuryl disulfide [FL-no: 13.144] and 2-furfuryl 3-oxo-2-butyl disulphide [FL-no: 13.185] a NOAEL for a comparable substance is not available. However, after fission of the disulphide bridge the resulting furan-containing fragment, which is more reactive than the disulphide itself, could be evaluated by comparison with the toxicity of furfuryl mercaptan [FL-no: 13.026] from subgroup IIb. The NOAEL of furfuryl mercaptan in a multiple dose level 91-day oral gavage study with rats was 3 mg/kg bw per day (Phillips et al., 1977). When the NOAEL for furfuryl mercaptan is compared with the estimated daily *per capita* intakes based on the MSDI approach expressed in µg/kg bw per day for methyl 5-methylfurfuryl disulfide [FL-no: 13.144] and 2-furfuryl 3-oxo-2-butyl disulphide [FL-no: 13.185], adequate margins of safety of 75×10^6 and 16×10^6, respectively, can be calculated.

The Panel noted that the candidate substance 3-(furfuryldithio)-2-methylfuran [FL-no: 13.178] is synonymous with [FL-no: 13.192]. The latter substance has been assigned the JECFA number 1524 in the report of the 69th meeting (JECFA, 2009). For this substance, in the JECFA evaluation, an MSDI for Europe of 0.24 µg *per capita* per day was given. This figure, which is higher and more recent than the exposure estimate in the previous version of this FGE (0.0012 µg *per capita* per day), will be used in the current revision of this FGE. The candidate substance 3-(furfuryldithio)-2-methylfuran [FL-no: 13.178] is structurally related to the supporting substance bis(2-methyl-3-furyl) disulfide [FL-no: 13.016], which has been tested in two single-dose-level 90-day dietary studies with rats at 5 mg/kg bw per day and 0.45 mg/kg bw per day, respectively (Oser, 1970a; Morgareidge and Oser, 1970a). Treatment-related effects were seen at the intake level of 5.0 mg/kg bw per day, but the intake level of 0.45 mg/kg bw per day was determined to be a NOAEL. The disulphide bridge fission products are related to [FL-no: 13.026] for which a NOAEL of 3 mg/kg bw per day has been derived. When the

estimated daily *per capita* intake based on the MSDI approach expressed in µg/kg bw per day of 3-(furfuryldithio)-2-methylfuran [FL-no: 13.178] is compared to this NOAEL an adequate margins of safety of 1.1×10^5 can be calculated.

Alternatively, the two fission products of 3-(furfuryldithio)-2-methylfuran [FL-no: 13.178] may be considered separately. These fission products are [FL-no: 13.055] and [FL-no: 13.026], for which NOAELs of 5 mg/kg bw per day and 3 mg/kg bw per day, respectively, have been derived (Oser, 1970b; Phillips et al., 1977). Exposure to [FL-no: 13.178] at the level of its MSDI would correspond to exposures to [FL-no: 13.026] and [FL-no: 13.055] of 0.12 µg per person per day for both fragments. Comparison of these exposure estimates to the NOAELs for these two fragments provides adequate margins of safety of 1.5×10^6 and 2.5×10^6 for [FL-no: 13.026] and [FL-no: 13.055], respectively.

Subgroup IId polysulphide [FL-no: 13.146]:

The one candidate flavouring substance in this subgroup methyl furfuryl trisulphide [FL-no: 13.146] is a trisulphide which may be anticipated to release perthiols upon metabolism. Similar reactive products may be anticipated for bis-(2-methyl-3-furyl)tetrasulphide [FL-no: 13.017] for which a NOAEL of 0.56 mg/kg bw per day in a 90-day study has been derived (Morgareidge and Oser, 1970b). Comparison of this NOAEL with the estimated daily *per capita* intake of methyl furfurul trisulphide [FL-no: 13.146] based on the MSDI approach expressed in µg/kg bw per day of 0.0024 µg provides an adequate margin of safety of 14×10^6.

Subgroup IIe thioester [FL-no: 13.135]:

The thiol released after hydrolysis of the candidate substance 1-(2-furfurylthio)propanone [FL-no: 13.135] is the supporting substance 2-furanmethanethiol [FL-no: 13.026] from subgroup IIb. The NOAEL of 2-furanmethanethiol in a multiple dose level 91-day oral gavage study with rats was 3 mg/kg bw per day (Phillips et al., 1977). Comparison of the NOAEL for 2-furanmethanethiol with the estimated daily *per capita* intake based on the MSDI approach expressed in µg/kg bw per day of 1-(2-furfurylthio)propanone provides an adequate margin of safety of 1.6×10^7.

Summary:

For the six, two, four, one and one substances in subgroups IIa, IIb, IIc, IId and IIe, respectively, which have been evaluated through the Procedure, it can be concluded at step B4 of the Procedure that these 14 candidate substances do not pose a safety concern when used as flavouring substances at the estimated levels of intake based on the MSDI approach.

6.3. EFSA considerations

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the candidate substances included in this FGE.

At step 1 the classification according to Cramer et al, 1977 was revised from class II to III for 11 of the flavouring substances [FL no: 13.033, 13.056, 13.065, 13.071, 13.079, 13.082, 13.142, 13.153, 13.160, 13.196 and 13.197]. These revisions were consistent with the classifications in the related FGE.13Rev2 and FGE.67Rev1, and do not change the routing of these substances through the Procedure. The Panel noted that differences between the conclusions reached for individual substances by the Panel and those reached by the JECFA do not result from the revisions of the classifications according to the Cramer system.

For 23 substances [FL-no: 13.016, 13.017, 13.026, 13.033, 13.040, 13.041, 13.050, 13.051, 13.053, 13.055, 13.065, 13.071, 13.075, 13.077, 13.078, 13.086, 13.152, 13.153, 13.015, 13.032, 13.063, 13.093 and 13.151] NOAELs could be identified at step B4 of the Procedure, either for the substances themselves, or for closely related substances. At step B4 it was concluded that these 23 substances

would not represent a safety concern at their estimated levels of intake as flavouring substance based on the MSDI approach.

For 10 substances the Panel did not agree with the JECFA with respect to the NOAEL used at step B4 of the Procedure:

S-methyl 2- furanthiocarboxylate [FL-no: 13.142]

For substance [FL-no: 13.142] the Panel considered that upon hydrolysis this substance would yield furoic acid and methylmercaptan in amounts of 0.29 and 0.13 µg per person per day, respectively, when the intake of [FL-no: 13.142] would equal the MSDI. In FGE.13Rev1 furoic acid has been evaluated by comparison with the ADI for furfural. This ADI is 0.5 mg/kg bw per day, equivalent to 30 mg per person per day. Thus, it is not anticipated that the exposure to furoic acid resulting from the hydrolysis of [FL-no: 13.142] would represent a safety concern. No NOAEL is available for the methylmercaptan fragment, but for the evaluation of this fragment the NOAEL of 6.7 mg/kg bw per day for [FL-no: 12.018; *S*-Ethyl acetothioate] found in a 90-day study by Shellenberger (Shellenberger, 1970) may be used. This NOAEL would represent a dose of 4 mg/kg bw per day of ethylmercaptan. When this value is compared to the exposure estimate of methylmercaptan resulting from intake of [FL-no: 13.142] at the estimated level of intake, an adequate margin of safety of 1.9×10^6 can be calculated.

The NOAEL for substance methyl 2-methyl-3-furyl disulfide [FL-no: 13.079] appeared to be invalid because the JECFA took this NOAEL from a study carried out with a structurally unrelated substance. Therefore the evaluation of this substance and the evaluation of three other substances [FL-no: 13.064, 13.082 and 13.197], which depended on this NOAEL, should be reconsidered.

Methyl 2-methyl-3-furyl disulfide [FL-no: 13.079]

For the candidate substance methyl 2-methyl-3-furyl disulfide [FL-no: 13.079] a NOAEL for a comparable substance is not available. However, after fission of the disulphide bridge the resulting furan-containing fragment is 2-methyl-3-furanthiol [FL-no: 13.055], which is more reactive than the disulphide itself. The NOAEL of 2-methyl-3-furanthiol in a multiple dose level 90-day oral gavage study with rats was 5 mg/kg bw per day (Oser, 1970b). When exposed to [FL-no: 13.079] at the level of the MSDI a maximum daily exposure to 2-methyl-3-furanthiol [FL-no: 13.055] of 0.52 µg per person per day can be calculated. When this exposure is compared with the NOAEL for 2-methyl-3-furanthiol an adequate margin of safety of 5.8×10^5 can be calculated. For the methylmercaptan fragment a margin of safety of 1.1×10^6 can be calculated in the same way as described above for [FL-no: 13.142].

Propyl 2-methyl-3-furyl disulfide [FL-no: 13.082]

For the candidate substance propyl 2-methyl-3-furyl disulfide [FL-no: 13.082] a NOAEL for a comparable substance is not available. However, after fission of the disulphide bridge the resulting furan-containing fragment is 2-methyl-3-furanthiol [FL-no: 13.055], which is more reactive than the disulphide itself. The NOAEL of 2-methyl-3-furanthiol in a multiple dose level 90-day oral gavage study with rats was 5 mg/kg bw per day (Oser, 1970b). When exposed to [FL-no: 13.082] at the level of the MSDI a maximum daily exposure to 2-methyl-3-furanthiol [FL-no: 13.055] of 0.07 µg per person per day can be calculated. When this exposure is compared with the NOAEL for 2-methyl-3-furanthiol an adequate margin of safety of 4.1×10^6 can be calculated. For the propylmercaptan fragment a margin of safety of 4.9×10^6 can be calculated in the same way as described above for the methylmercaptan fragment of [FL-no: 13.142].

Methyl-furfuryl disulfide [FL-no: 13.064]

For the candidate substance methyl furfuryl disulfide [FL-no: 13.064] a NOAEL for a comparable substance is not available. However, after fission of the disulphide bridge the resulting furan-containing fragment is 2-furanmethanethiol [FL-no: 13.026], which is more reactive than the disulphide itself. The NOAEL of 2-furanmethanethiol in a multiple dose level 91-day oral gavage study with rats was 3 mg/kg bw per day (Phillips et al., 1977). When exposed to [FL-no: 13.064] at the level of the MSDI a maximum daily exposure to 2-furanmethanethiol of 0.61 µg per person per day can be calculated. When this exposure is compared with the NOAEL for 2-furanmethanethiol an adequate margin of safety of 3×10^5 can be calculated. For the methylmercaptan fragment a margin of safety of 9.4×10^5 can be calculated in the same way as described above for the methylmercaptan fragment from [FL-no: 13.142].

Furfuryl propyl disulfide [FL-no: 13.197]

For the candidate substance furfuryl propyl disulfide [FL-no: 13.197] a NOAEL for a comparable substance is not available. However, after fission of the disulphide bridge the resulting furan-containing fragment is 2-furanmethanethiol [FL-no: 13.026], which is more reactive than the disulphide itself. The NOAEL of 2-furanmethanethiol in a multiple dose level 91-day oral gavage study with rats was 3 mg/kg bw per day (Phillips et al., 1977). When exposed to [FL-no: 13.197] at the level of the MSDI a maximum daily exposure to 2-furanmethanethiol of 0.15 µg per person per day can be calculated. When this exposure is compared with the NOAEL for 2-methyl-3-furanthiol an adequate margin of safety of 12×10^6 can be calculated. For the propylmercaptan fragment a margin of safety of 24×10^6 can be calculated in the same way as described above for the methylmercaptan fragment from [FL-no: 13.142].

4-(Furfuryl-thio)-pentan-2-one [FL-no: 13.196]

The Panel noted that the name and structure of the JECFA substance 1084 as presented in JECFA (JECFA, 2003) were inconsistent with the CAS number provided for this substance. After correspondence with Industry, the correct name and structure were provided (see Table 1). As the substance with the corrected name and structure deviates substantially from the substance evaluated by the JECFA, this substance has to be reconsided at step B4 of the Procedure. A NOAEL for substance [FL-no: 13.196] was not identifed. The Panel considered this substance to be structurally related to the supporting substance 3-[(2-methyl-3-furyl)thio]-4-heptanone [FL-no: 13.077]. For this substance a NOAEL of 3.76 mg/kg bw per day could be derived from a 90 day dietary single dose level study in rats (Gallo et al., 1976b). When the exposure estimate for 4-(furfurylthio)-pentan-2-one [FL-no: 13.196] at the level of the MSDI (0.012 µg *per capita* per day) is compared to this NOAEL an adequate margin of safety of 18.8×10^6 can be calculated.

[FL-no: 13.160, 13.193 and 13.194]

For three substances [FL-no: 13.160, 13.193 and 13.194] the Panel disagreed with the JECFA with respect to the proposed use of the NOAEL for [FL-no: 13.086] because the Panel considered the tetrahydrofuran ring in [FL-no: 13.160, 13.193 and 13.194] not sufficiently similar to the dihydrofuran ring in [FL-no: 13.086]. Therefore a NOAEL supporting these three substances was not available, and the Panel requested a new 90-day repeated dose toxicity study with the representative substance, 2,5-dimethyltetrahydro-3-furylthiol acetate [FL-no: 13.194]. In response to this request expressed in FGE.65, the Flavour Industry has now submitted a range-finding 14-day study and a 90-day study in rats (the 90-day toxicity study is summarised in Section 6) with substance [FL-no: 13.160]. The Panel accepted the arguments provided by EFFA (see the section 'Background as provided by the European Commission') to support the submission of testing results with a different representative substance. Based on this new study the Panel could derive a NOAEL of 5 mg/kg bw per day. When the exposure estimates, based on MSDI for the three substances [FL-no: 13.160, 13.193 and 13.194] of 55, 0.012, or

0.012µg *per capita* per day are compared to the NOAEL of 5 mg/kg bw per day for [FL-no: 13.160], adequate margins of safety of 5400, 2.5×10^7 or 2.5×10^7 or can be calculated, respectively.

Difurfuryl sulfide [FL-no: 13.056]

For difurfuryl sulfide [FL-no: 13.056] the Panel decided that the available NOAEL from a 14-day study was inappropriate to draw a conclusion on its safety when used as a flavouring substance.

CONCLUSION

The present evaluation deals with 33 substances in the JECFA flavouring group of sulfur-substituted furan derivatives. These substances are structurally related to the group of sulfur-substituted furans evaluated within the group of 'Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14' evaluated by EFSA in FGE.13Rev2.

The present revision of FGE.65, FGE.65Rev1 is due to the availability of new toxicity data on 2-methyltetrahydrofuran-3-thiol [FL-no: 13.160], requested by the Panel in FGE.65.

The Panel agrees with the way the application of the Procedure has been performed by the JECFA for the candidate substances included in this FGE. For 23 substances the Panel also agreed with JECFA with respect to the choice of the NOAEL to finalise the evaluation. For nine substances the NOAEL used by JECFA was considered invalid, but the Panel could finalise the evaluations of these substances using NOAELs derived from new or existing data either for the candidate substances or forsupporting substances. Thus, for 32 substances the Panel reached the same conclusion as JECFA with respect to their use as chemically defined flavouring substances in food. For one substance [FL-no: 13.056] no adequate NOAEL could be identified by the Panel and subsequently, no conclusion as to the safety when used at levels of intake estimated using the MSDI approach could be reached.

For all 33 substances evaluated through the Procedure by JECFA use levels are needed to calculate the mTAMDIs in order to identify those flavouring substances that need more refined exposure assessment and to finalise the evaluation.

In order to determine whether the conclusion for the 33 JECFA evaluated substances can be applied to the materials of commerce, it is necessary to consider the available specifications: Adequate specifications including complete purity criteria and identity are available for all of the JECFA evaluated substances.

Thus, the Panel has reservations for one substance [FL-no: 13.056] for which additional toxicity data are needed. The Panel is aware, that data for [FL-no: 13.056] were not submitted before the deadline as indicated in Commission Implementing Regulation (EC) No 872/2012. The Commission has communicated that this substance is in the process of being deleted from the Union List. For the remaining 32 JECFA evaluated sulfur-substituted furan derivatives [Fl-nos: 13.015, 13.016, 13.017, 13.026, 13.032, 13.033, 13.040, 13.041, 13.050, 13.051, 13.053, 13.055, 13.056, 13.063, 13.064, 13.071, 13.075, 13.077, 13.078, 13.079, 13.082, 13.086, 13.093, 13.142, 13.151, 13.152, 13.153, 13.160, 13.193, 13.194, 13.196 and 13.197], the Panel agrees with JECFA conclusion 'No safety concern at estimated levels of intake as flavouring substances' based on the MSDI approach.

SUMMARY OF TOXICITY DATA

Table 3: Toxicity data considered by the Panel in FGE.65Rev1

Chemical Name [FL-no:]	Species; Sex No/group	Route	Doses (mg/kg bw per day)	Duration (days)	NOAEL (mg/kg bw per day)	Reference	Comments
2-Methyltetrahydrofuran-3-thiol [13.160]	Rat; M, F 3	Diet	0, 75, 500 and 1000	14	75	(Kappeler, 2013)	
	Rat; M, F 3	Gavage	0, 5, 55 and 125	90	5	(Kappeler, 2014)	

SUMMARY OF SAFETY EVALUATIONS

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

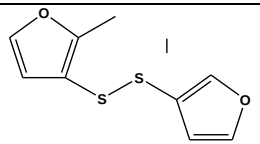
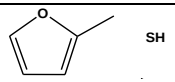
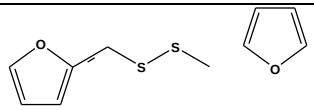
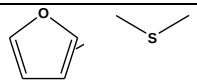
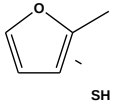
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (μg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.016 1066	bis-(2-Methyl-3-furyl) disulfide		0.27 0.7	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.026 1072	2-Furanmethanethiol		29 11	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.050 1081	Difurfuryl disulfide		3.3 0.7	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.053 1076	Methyl furfuryl sulfide		0.97 0.1	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.055 1060	2-Methylfuran-3-thiol		0.52 0.9	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '95' and secondary components 'Bis(2-methyl-3-furyl)disulfide'. No safety concern at the estimated level of intake based on the MSDI approach.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

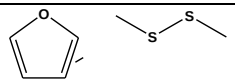
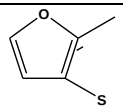
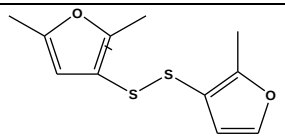
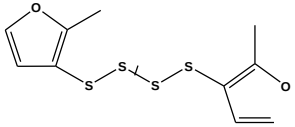
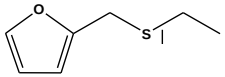
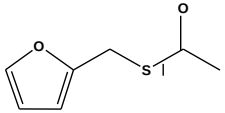
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.064 1078	Methyl furfuryl disulfide		0.85 0.04	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.152 1061	2-Methyl-3-(methylthio)furan		1.2 0.1	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.015 1067	bis-(2,5-Dimethyl-3-furyl) disulfide		0.012 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.017 1068	bis-(2-Methyl-3-furyl) tetrasulfide		0.97 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.032 1077	Furfuryl isopropyl sulfide		0.0012 0.1	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.033 1074	*S*-Furfuryl acetothioate		0.43 0.05	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

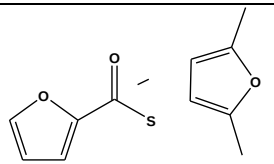
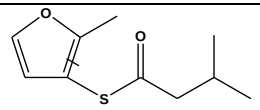
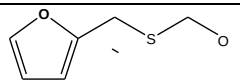
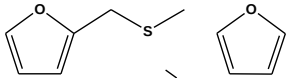
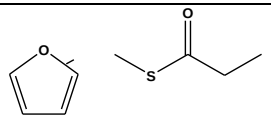
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.040 1071	(*S*)-2,5-Dimethyl-3-thiofuroylfuran		0.012 0.01	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	JECFA evaluated (*S*)-2,5-dimethyl-3-thiofuroylfuran (CASrn as in Register). No safety concern at the estimated level of intake based on the MSDI approach.
13.041 1070	2,5-Dimethyl-3-(isopentylthio)furan		0.49 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	Registername to be changed to 2,5-dimethyl-3-(isovalerylthio)furan. No safety concern at the estimated level of intake based on the MSDI approach.
13.051 1073	*S*-Furfuryl thioformate		1.3 0.02	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.056 1080	Difurfuryl sulfide		0.73 0.005	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	Toxicity data are required. No adequate NOAEL exists.	The Panel is aware that data were not submitted before the deadline as indicated in Commission Implementing Regulation (EC) No 872/2012. The Commission has communicated that this substance is in the process of being deleted from the Union List.
13.063 1075	*S*-Furfuryl propanethioate		0.012 0.005	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

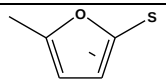
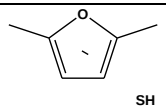
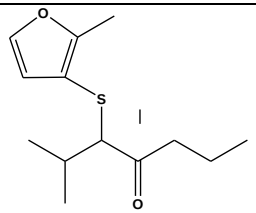
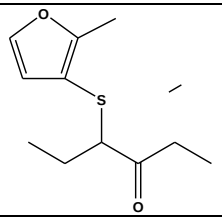
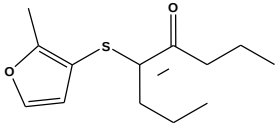
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.065 1062	2-Methyl-5-(methylthio)furan		1.1 0.02	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.071 1063	2,5-Dimethylfuran-3-thiol		0.024 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.075 1086	2,6-Dimethyl-3-((2-methyl-3-furyl)thio)heptan-4-one		1.8 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '94' and secondary components '2,6-Dimethyl-2-[(2-methyl-3-furyl)thio]-4-heptanone'. No safety concern at the estimated level of intake based on the MSDI approach.
13.077 1085	3-((2-Methyl-3-furyl)thio)heptan-4-one		2.9 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.078 1087	4-((2-Methyl-3-furyl)thio)nonan-5-one		0.73 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

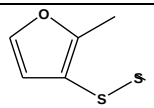
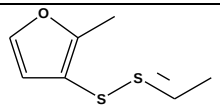
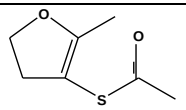
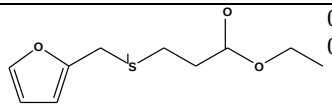
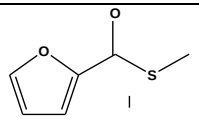
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (μg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.079 1064	Methyl 2-methyl-3-furyl disulfide		0.73 0.05	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '97' and secondary components 'up to 3% bis(2-methyl-3-furyl)disulfide'. No safety concern at the estimated level of intake based on the MSDI approach.
13.082 1065	Propyl 2-methyl-3-furyl disulfide		0.12 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '97' and secondary components 'up to 2% bis(2-methyl-3-furyl)disulfide and propyl disulfide'. No safety concern at the estimated level of intake based on the MSDI approach.
13.086 1089	4,5-Dihydro-2-methyl-3-thioacetoxyfuran		0.49 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.093 1088	Ethyl 3-(2-furfurylthio)propionate		0.012 0.2	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.142 1083	*S*-Methyl 2-furanthiocarboxylate		0.37 0.1	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

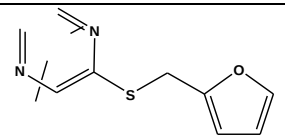
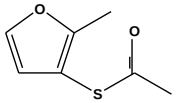
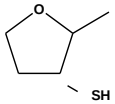
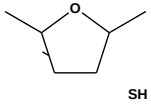
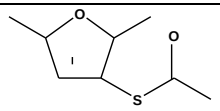
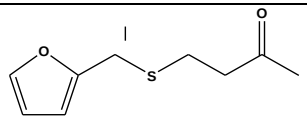
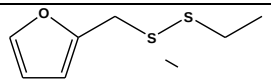
FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.151 1082	2-Methyl-3,5 and 6-(furfurylthio)pyrazine	 2 or 5 or 6 -Methyl-3-(furfurylthio)pyrazine	0.37 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '99' and 'Mixture of isomers: 70 % 2,3-; 29 % 2,6-; trace 2,5-'. No safety concern at the estimated level of intake based on the MSDI approach.
13.153 1069	2-Methyl-3-furyl thioacetate		0.012 0.07	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	According to JECFA: Min. assay value is '92' and secondary components '*cis*- and *trans*-2-Methyl-3-tetrahydrofuranthiol acetate'.
13.160 1090	2-Methyltetrahydrofuran-3-thiol		55 0.7	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI.	According to JECFA: Min. assay value is '97' and '71 % *trans* and 26 % *cis* isomer'.
13.193 1091	2,5-Dimethyltetrahydro-3-furanthiol		0.012 0.9	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI.	According to JECFA: Min. assay value is '96 (mixture of 4 stereoisomers)'. Composition of stereoisomeric mixture to be specified.

Table 4: Summary of safety evaluation by the JECFA (JECFA, 2003)

FL-no JECFA-no	EU Register name	Structural formula	EU MSDI[(a)] US MSDI (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	EFSA conclusion on the named compound[(f)]	EFSA conclusion on the material of commerce
13.194 1092	2,5-Dimethyltetrahydro-3-furyl thio acetate		0.012 2	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI.	According to JECFA: Min. assay value is '90 (mixture of 4 stereoisomers)' and secondary components '2,5-Dimethyltetrahydrofuran-3-thiol, Dimethyltetrahydro-3-furyl dithioacetate'. Composition of stereoisomeric mixture to be specified.
13.196 1084	4-[(2-Furanylmethyl)thio]-2-pentanone		0.012 0.6	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.
13.197 1079	Furyl propyl disulfide		0.024 3	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	No safety concern at the estimated level of intake based on the MSDI approach.	No safety concern at the estimated level of intake based on the MSDI approach.

(a): EU MSDI: Amount added to food as flavour in (kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita per day.
(b): Thresholds of concern: Class I = 1800 µg/person per day, Class II = 540 µg/person per day, Class III = 90 µg/person per day.
(c): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(d): No safety concern based on intake calculated by the MSDI approach of the named compound.
(e): Data must be available on the substance or closely related substances to perform a safety evaluation.
(f): Procedure steps, intake estimates, NOAEL, genotoxicity.

Table 5: Summary of safety evaluation by the EFSA/FGE.13Rev2 (EFSA CEF Panel, 2011)

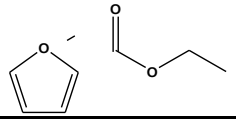
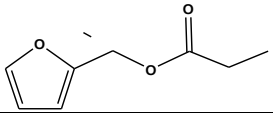
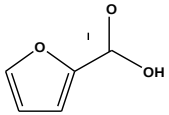
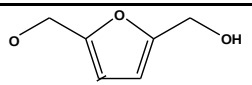
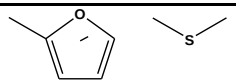
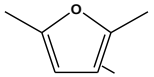
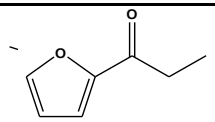
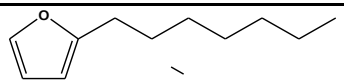
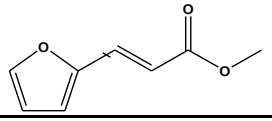
FL-no	EU Register name	Structural formula	MSDI[(a)] (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	Outcome on the material of commerce[(f),(g),(h)]	Evaluation remarks
13.122	Ethyl 2-furoate		0.39	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.130 759	Furfuryl butyrate		0.24	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.136	2-Furoic acid		0.013	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.139	5-Hydroxymethylfurfural dehyde		0.39	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.145	Methyl 5-methylfurfuryl sulfide		0.0024	Class II B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.125	2-Ethyl-5-methylfuran		0.011	Class II No evaluation			Concern for genotoxicity.
13.155	2-Methyl-5-propionylfuran		0.011	Class II No evaluation			Concern for genotoxicity. No longer supported by Industry (DG SANCO, 2012).
13.162	2-Octylfuran		0.011	Class II No evaluation			Concern for genotoxicity.
13.011	Ethyl furfuracrylate		0.12	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 5: Summary of safety evaluation by the EFSA/FGE.13Rev2 (EFSA CEF Panel, 2011)

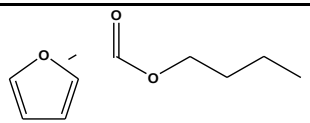
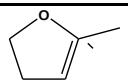
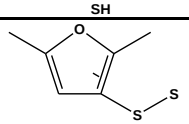
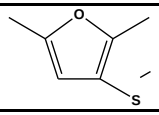
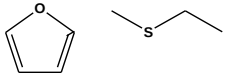
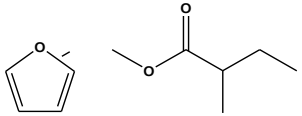
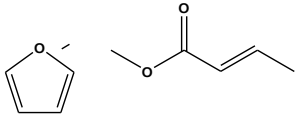
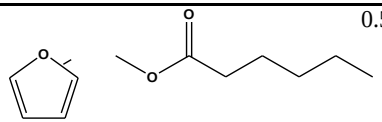
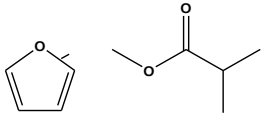
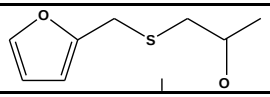
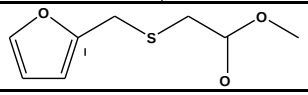
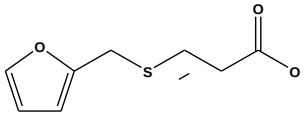
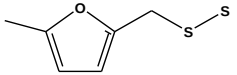
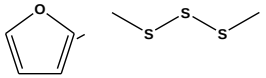
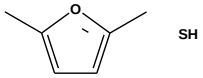
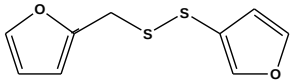
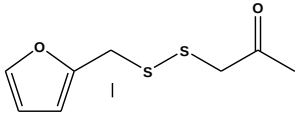
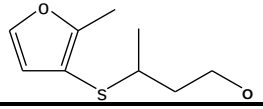
FL-no	EU Register name	Structural formula	MSDI[(a)] (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	Outcome on the material of commerce[(f),(g),(h)]	Evaluation remarks
13.102	Butyl 2-furoate		0.12	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.108 2097	4,5-Dihydro-3-mercapto-2-methylfuran		37	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.113	2,5-Dimethyl-3-(methyldithio)furan		0.0012	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.114	2,5-Dimethyl-3-(methylthio)furan		0.0024	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.124	Ethyl furfuryl sulfide		0.18	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.127	Furfuryl 2-methylbutyrate		0.73	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.129	Furfuryl but-2-enoate		0.11	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.132	Furfuryl hexanoate		0.58	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.133	Furfuryl isobutyrate		0.89	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

Table 5: Summary of safety evaluation by the EFSA/FGE.13Rev2 (EFSA CEF Panel, 2011)

FL-no	EU Register name	Structural formula	MSDI[(a)] (µg/*capita* per day)	Class[(b)] Evaluation procedure path[(c)]	Outcome on the named compound[(d),(e)]	Outcome on the material of commerce[(f),(g),(h)]	Evaluation remarks
13.135 2096	1-(2-Furfurylthio)propanone		0.61	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.141	Methyl (2-furfurylthio)acetate		0.011	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.143	Methyl 3-(furfurylthio)propionate		0.011	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.144	Methyl 5-methylfurfuryl disulfide		0.0024	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.146	Methyl furfuryl trisulfide		0.0024	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.149	5-Methyl-2-furanmethanethiol		0.37	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.178 1524	3-(Furfuryldithio)-2-methylfuran		0.24	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.185	2-Furfuryl 3-oxo-2-butyl disulphide		0.011	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	
13.199 2095	3-[(2-Methyl-3-furyl)thio]-butanal		1.2	Class III B3: Intake below threshold, B4: Adequate NOAEL exists	d	f	

(a): EU MSDI: Amount added to food as flavour in (kg / year) x 109 / (0.1 x population in Europe (= 375 x 106) x 0.6 x 365) = µg/capita per day.
(b): Thresholds of concern: Class I = 1800 µg/person per day, Class II = 540 µg/person per day, Class III = 90 µg/person per day.
(c): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot.
(d): No safety concern based on intake calculated by the MSDI approach of the named compound.

(e): Data must be available on the substance or closely related substances to perform a safety evaluation.
(f): No safety concern at the estimated level of intake of the material of commerce meeting the specification requirement (based on intake calculated by the MSDI approach).
(g): Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.
(h): No conclusion can be drawn due to lack of information on the purity of the material of commerce.

DOCUMENTATION PROVIDED TO EFSA

1. EFFA (European Flavour Association), 2014a. Addendum of Additional Data Relevant to the Flavouring Group Evaluation of the Chemical Group 14 (Annex I of 1565/2000/EC) Sulfur Substituted Furan Derivatives from Chemical Group 14 Flavouring Group Evaluation 65, Consideration of Sulfur Substituted Furan Derivatives used as Flavouring Agents Evaluated by JECFA (59th meeting) Structurally Related to a Subgroup of Substances within the group of 'Furfuryl and Furan Derivatives with and without Additional Side-chain Substituents and Heteroatoms from Chemical Group 14' evaluated by EFSA in FGE.13Rev1 (2009). Addendum to FGE.65. 1/3/2014. FLAVIS/8.248.

2. EFFA (European Flavour Association), 2014b. E-mails from EFFA to FLAVIS Secretariat, Danish Food Institute, Technical University of Denmark. Dated 3 and 7 October 2014. Information on substances [FL-no: 13.086, 13.193 and 13.194] in FGE.86Rev2. FLAVIS/8.252.

3. Kappeler KV, 2013. A 14-Day Oral (Dietary) Toxicity Study of 2-Methyltetrahydrofuran-3-thiol in Rats. WIL Research. Study no. WIL-968010. 23 July 2013. Unpublished report.

4. Kappeler KV, 2014. A 90-Day Oral (Gavage) Toxicity Study of 2-Methyltetrahydrofuran-3-thiol in Rats. WIL Research. Study no. WIL-968011. 21 August 2014. Unpublished report.

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ABBREVIATIONS

ALP	Alkaline phosphatase
CAS	Chemical Abstract Service
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CoE	Council of Europe
EFSA	The European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good laboratory practise
ID	Identity
IR	Infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
No	Number
NOAEL	No observed adverse effect level
NOEL	No observed effect level
SCF	Scientific Committee on Food
WHO	World Health Organization